



An overview of the biology and viral pathogenesis of lymphoproliferative disorders in HIV-infected patients

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Introduction

Immunodeficiency (whether congenital, iatrogenic, or caused by infection) increases the risk of some types of cancer, especially malignancies etiologically linked to DNA tumor viruses, such as herpesviruses and polyomavirus.¹⁻⁴ Indeed, immunosuppression associated with HIV infection substantially increases the risk of developing Kaposi's sarcoma and non-Hodgkin's lymphoma. These two malignancies and invasive cervical carcinoma are the only recognized AIDS-defining cancers.⁵ Hodgkin's lymphoma was not included as an AIDS-defining illness by the Center for Disease Control and Prevention HIV classification system,⁵ but data from several studies suggest that the risk of Hodgkin's lymphoma in persons with HIV infection is increased.⁶⁻⁹

The introduction of highly active antiretroviral therapy (HAART) and prophylaxis against opportunistic diseases has significantly improved the survival of patients with HIV infection.^{10,11} HAART can cause a significant and sustained decrease in peripheral blood HIV RNA levels, as well as an increase in CD4 T cells.¹²⁻¹⁵ However, the influence of this therapy on AIDS-related lymphoproliferative disorders is less clear.^{16,17} Recent data from the United States and Western Europe have shown no significant decrease in the incidence of non-Hodgkin's and Hodgkin's lymphomas, in contrast to dramatic reductions in Kaposi's sarcoma among patients treated with HAART.^{11,18-26} A meta-analysis of the incidence of cancers from selected cohorts²⁷ of HIV-infected patients from the periods of 1992 to 1996 and 1997 to 1999 by the International Collaboration on HIV and Cancer suggested a small decrease in systemic diffuse large cell lymphoma but no decrease

es in other types of non-Hodgkin's lymphoma. However, the analysis of lymphomas is limited by the lack of specific pathology information from some of the cohorts included in the meta-analysis.

While the goal of antiretroviral therapy is the suppression of HIV replication,^{28,29} failure to accomplish this objective is common in clinical practice, occurring at a rate of 40% to 70%.³⁰⁻³² Also, data suggest that the continuing efficacy of present antiretroviral therapy may allow more HIV-infected patients to survive with long-term mild to moderate immunosuppression, thereby placing such patients at risk for the development of lymphoproliferative disorders such as Hodgkin's and non-Hodgkin's lymphomas. Indeed, recent data suggest that 23% to 50% of patients receiving HAART developed Hodgkin's and non-Hodgkin's lymphomas despite effective HIV suppression and high CD4 T cell counts.^{25,26,33-36} These results substantiate that the development of lymphomas in HIV-infected individuals is a complex process not determined by HIV replication. In this review, we examine advances in understanding the biology and viral pathogenesis of lymphoproliferative disorders among HIV-infected patients.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is a common malignancy in HIV-infected patients and its incidence in that population may be increased up to 300 times.^{9,12,13} NHL incidence increases markedly with progression of HIV infection, although association with the level of CD4 lymphopenia is less pronounced than with other opportunistic infections. All populations at risk for HIV are also at risk for

the development of lymphoma, in contrast to Kaposi's sarcoma, which is diagnosed primarily in homosexual or bisexual men. The NHL that occurs in HIV-infected patients can be divided into two categories: systemic and primary central nervous system lymphoma (see Table). The genetic alterations of systemic NHL among HIV-infected patients include activation of oncogenes by chromosomal translocations (ie, *c-myc* and *bcl-2*) and/or inactivation of tumor suppressor genes (ie, p53).³⁷ A recent analysis showed that, compared to HIV-negative cases, NHL among HIV-infected patients was more likely to be highly proliferative and to express p53.³⁶ These data suggest a different pathogenesis of NHL among HIV-infected patients as compared to uninfected patients.

Some NHL in HIV-infected patients has been attributed to deficient immune surveillance of oncogenic herpesviruses, such as Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8), or perhaps to chronic antigenic stimulation and defective immune regulation.^{1,38} EBV is suspected of playing a major causative role in primary central nervous system (CNS) NHL in HIV-infected patients, as most of those tumors contain EBV DNA, but it is detected less frequently (<40%) in systemic NHL in HIV-infected patients³⁸ (see Table). EBV is found even less commonly in NHL from HIV-negative patients. HHV-8 is specifically associated with multicentric Castleman's disease and primary effusion lymphoma, which often occurs in a setting of profound immunosuppression.³⁸

As EBV and HHV-8 are absent from many forms of NHL, other viral agents such as polyomavirus simian virus 40 (SV40) have been investigated. Early studies reported the detection of polyomavirus SV40 DNA sequences in NHL from HIV-infected and non-HIV-infected patients, but the small size of the study populations, the lack of screening for other tumor viruses, and the limited confirmation of the detected viral sequences made it difficult to assess whether SV40 was associated with NHL.^{39,40}

However, recent large and controlled studies demonstrated that SV40 tumor antigen (T-ag) DNA sequences were significantly associated with NHL in both HIV-infected and non-HIV-infected patients.^{3,4,41} In addition, EBV was found to be associated with 39% of systemic NHL from HIV-infected patients and with only 15% from the HIV-negative group,³ similar to rates reported previously.³⁸ Importantly, the observation of minimal instances of co-infection with SV40 and EBV and the lack of detection of SV40 in nonmalignant lymphoid samples and cancer control specimens suggest that SV40 may be contributing to the development of some NHL among HIV-infected patients.³

The lymphomagenic capacity of SV40 is well-established in laboratory animal models. In hamsters inoculated intravenously with SV40, lymphomas developed among 72% of the animals, compared to none in the control group.⁴² The lymphomas were of B cell origin as they expressed cell surface antigen and their histology was consistent with diffuse large cell type.⁴³ An etiologic role for the virus in the development of lymphomas was supported because SV40 T-ag was expressed in all tumor cells, animals with tumors developed antibody against SV40 T-ag, and neutralization of SV40 with specific antibody before virus inoculation prevented lymphoma development.⁴² SV40 oncogenesis is mediated in large part by the viral oncoprotein, T-ag, as a result of its binding and inactivation of tumor suppressor proteins in the p53 and pRb families.¹ The functional inactivation of these two important cell cycle control proteins stimulates host cells to proliferate. Other cellular effects may be mediated by SV40 in human B cells as well.^{44,45} Further studies are needed to define the mechanisms of SV40 interactions with human lymphocytes.

Hodgkin's lymphoma

The association between HIV infection and the development of Hodgkin's lymphoma, which typically occurs in the age groups of patients most affected by HIV, has been slowly established because this

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malignancy is an uncommon cancer. An analysis⁷ of AIDS and cancer registry data from diverse regions of the United States conducted between 1978 and 1996 showed that Hodgkin's lymphoma occurred in a statistically significant excess in HIV-infected patients (relative risk [RR] 11.5; 95% confidence interval [95% CI], 10.6–12.5). More importantly, that analysis indicated a particular association with Hodgkin's lymphoma subtypes of mixed cellularity (RR, 18.3; 95% CI, 15.9–20.9) and lymphocyte depletion (RR, 35.3; 95% CI, 24.7–48.8).

There are very few studies that have analyzed Hodgkin's lymphoma during the HAART era,^{10,20,24} so assessing the incidence of this malignancy in HIV-infected patients since the introduction of HAART has been difficult. However, a recent investigation²⁶ showed that Hodgkin's lymphoma has a low incidence in HIV-infected patients receiving HAART (6.5 per 1,000 patients) and that no significant difference in the incidence of this malignancy was observed between patients receiving HAART and those naïve to antiretroviral therapy. The results further suggested that Hodgkin's lymphoma is an aggressive disease with unfavorable clinical outcome in HIV-infected patients.²⁶ Reports prior to the introduction of HAART described HIV-related Hodgkin's lymphoma as an atypical and more aggressive form of disease with unusual presentation and worse outcome compared with Hodgkin's lymphoma in patients with HIV-negative status.^{6-9,12} Hodgkin's lymphoma in persons with HIV infection presented at an advanced stage, and commonly at extranodal sites. Mixed cellularity and lymphocyte depletion subtypes accounted for a greater proportion of the cases, and nodular sclerosing subtype for a lower proportion of cases, than in persons without HIV infection.^{6-9,12} Recent data indicate that mixed cellularity and lymphocyte depletion subtypes continue to be the most frequent types of Hodgkin's lymphoma and that diffuse disease remains a common feature of this malignancy in the HAART era.²⁶ These clinical and histopathologic features of

Hodgkin's lymphoma among HIV-infected patients may be the result of the alterations of CD4 T cells in this patient population.

In non-HIV-infected patients with Hodgkin's lymphoma, CD4 T cells predominate in the tumor microenvironment and may contribute, at least in part, to the modulation of the Hodgkin's lymphoma phenotype⁴⁶ and eventually to its clinical behavior.^{47,48} In contrast, among patients with HIV infection, the tumor microenvironment reportedly lacks the typical high proportion of CD4 T cells that may keep tumor cells and tissues under control and is characterized by an unusually high proportion of malignant cells.^{12,49} Indeed, studies both prior to the introduction of HAART and in patients receiving HAART indicate that Hodgkin's lymphoma tends to develop in patients with a median CD4 T cell count of 200 cells/mm³.^{6-9,12,26}

Immunodeficiency can play a negative role both in the clinical presentation and the outcome of HIV-infected patients with lymphoma.²⁶ A recent study compared the clinical features and prognosis of Hodgkin's lymphoma and NHL among HIV-infected patients.⁵⁰ The clinical presentation of these two lymphoproliferative disorders was similar, except for the decreased frequency of extranodal disease that was seen in patients with Hodgkin's lymphoma as compared to NHL (56% vs. 82%, $p=0.02$) and the increased frequency of bone marrow involvement in patients with Hodgkin's lymphoma as compared to NHL (50% vs. 20%, $p=0.01$). Complete remission and overall survival rates did not differ significantly, with estimated overall survival at 5 years of 24% in HIV-infected patients with Hodgkin's lymphoma and 23% in patients with NHL.

Data indicate that 50% of the patients with Hodgkin's lymphoma who were receiving HAART had detectable HIV RNA viral loads.²⁶ These findings support the hypothesis that factors promoting the development of lymphomas may not be related

to immune dysfunction or may be associated with processes not affected by HAART. Indeed, EBV is suspected of playing a causative role in Hodgkin's lymphoma: as many as 70% of Reed-Sternberg cells are EBV-positive in HIV-infected patients, whereas only about one-third of these malignancies in the general population are EBV-positive²⁶ (see Table). The precise role of EBV in Hodgkin's lymphoma among HIV-infected patients, however, requires further investigation.

Conclusion

Recent investigations suggest that Hodgkin's lymphoma and systemic NHL are significant causes of mortality among HIV-infected patients during the

HAART era. As antiretroviral therapies improve the survival of HIV-infected patients, the risk of developing or dying from cancer may increase. Large and well-designed population-based studies will be needed to better define the spectrum of malignancies and the most effective strategies for screening and treatment in HIV-infected patients. In addition, further research is essential to define the role of DNA tumor viruses in the genesis of lymphoproliferative disorders among these patients.



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Table. Characteristics of non-Hodgkin's and Hodgkin's lymphoma in patients with HIV infection during the HAART era.

Characteristics	Systemic-NHL	Primary CNS-NHL	Hodgkin's Lymphoma	Other
Histology	Diffuse large B-cell and Burkitt's	Diffuse large B-cell		–
Median CD4 T cell count	~200 cells/mm ³	<50 cells/mm ³	~200 cells/mm ³	–
Incidence (per 1000 patients)	3.6 – 17	ND	6.5	–
EBV DNA in tumors	< 40%	~100%	~70%	–
SV40 DNA in tumors	0% – 40%	ND	< 10%	–
HHV-8 DNA in tumors	< 5%	0	0	Primary effusion lymphoma (100%) Castleman's disease (100%)

Abbreviations: NHL, non-Hodgkin's lymphoma; CNS, central nervous system; HAART, highly active antiretroviral therapy; EBV, Epstein-Barr virus; SV40, simian virus 40; HHV-8, human herpesvirus 8; ND, not determined.

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